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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
GOLDBERG, JEANINE ANNE

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 09/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/810,993	GILAD ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *2,3,5-10,12-19,21 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,11 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *102; 902* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed July 28, 2003. Currently, claims 1-22 are pending. Claims 2-3, 5-10, 12-19, 21-22 have been withdrawn as drawn to non-elected subject matter. Claims 1, 4, 11, 20 have been examined on the merits.

Election/Restrictions

2. Applicant's election with traverse of Group I, mutation of T2119C, claims 1, 4, 11, 20 in the paper filed July 28, 2003 is acknowledged. The response traverses the restriction requirement because the response asserts that the inventions are not independent. This is not found persuasive because dependent inventions may be properly restricted if they are distinct. As discussed in MPEP 803, one of the two criteria for requirement of restriction is that the "inventions must be independent (see MPEP 802.01, 806.04, 808.01) or distinct as claimed". Accordingly, the demonstration of distinctness of the inventions is sufficient grounds for restriction. As stated in MPEP 802.01 “(t)he law has long been established that dependent inventions (frequently termed related inventions) such as those used for illustration above may be properly divided if they are, in fact “distinct” inventions, even though dependent”.

Applicants further argue that it would not be an undue burden to examine the claims of all groups I-II. However, it is maintained that undue burden would be required to examine the claims of groups II along with the claims of group I as evidenced by the fact that the claims of groups I, II have acquired a separate status in the art as recognized by their different classification and as recognized by their divergent subject

matter and because a search of the subject matter of invention I is not co-extensive with a search of inventions II.

Moreover, the response traverses the requirement of one marker/sequence. The traversal is on the grounds that the claims are all directed to single mutation in the same gene for the same disease, thereby constituting a single invention. This argument has been thoroughly reviewed, but is not found persuasive because a search for the first mutation is not coextensive of a search for the second mutation. As previously provided in the restriction requirement, applicant may clearly provide on the record that the mutations are obvious variants if applicants believe that the markers are not separately patentable. However, currently, it is maintained that the claimed markers constitute independent and distinct inventions.

The requirement is still deemed proper and is therefore made FINAL.

Claims 2-3, 5-10, 12-19, 21-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. This application contains claims 2-3, 5-10, 12-19, 21-22 are drawn to an invention nonelected with traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Priority

3. This application claims priority to provisional application 60/189,761, filed March 16, 2000.

Drawings

4. The drawings are acceptable.

Specification

5. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The instant abstract is longer than 150 words. Additionally, the abstract is not clear and concise.

Claim Objections

6. Claims 1, 4 are objected to because the claim contains more than one period. For example, SEQ. ID. NO: 1 contains two periods and the end of the claim contains a period. As provided in the MPEP 2422:

> (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing " in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

This objection may be overcome by amending SEQ. ID. NO: 1 to read SEQ ID NO: 1 (see MPEP 608.01(m)).

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 4, 11, 20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working

> examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 1, 4, 11 and 20 are directed to methods of detecting polymorphisms within the ATM gene which are indicative of a predisposition to developing breast cancer. Specifically, Applicants have elected the polymorphism at position 2119 which causes a change from T to C.

The invention is in class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Teachings of the Specification and the presence of Working Examples

The specification teaches the "presence of such a mutation indicates that the subject has a predisposition for developing primary or bilateral breast cancer" (page 5, lines 20-25). The specification provides Example 1 to determine whether germline sequence variations in ATM influence: 1. breast cancer risk; 2. bilaterial breast cancer risk and 3. response to radiation therapy (page 5-7). Table 3 provides the ATM sequence variations in BC/BC patients. It is noted that only a single patient contains the elected polymorphism at position 2119, namely patient number 138 (page 18). Table 4 illustrates an analysis of mutations found in the cohort of BC-BC patients and normal individuals. There does not appear to be any data present for MSKO primary BC. As seen on page 20 of the specification, the 2119 mutation is found in 2/70 BC-BC individuals and 2/63 normal individuals. Thus, the percentage of times the mutation was found in breast cancer patients was lower than in normal individuals. Table 5 illustrates the sequence variation in the healthy controls. Control individuals number 46 and 47 both had the 2119 variation (page 22).

The specification has no working examples of an association between the presence of the mutation and indicia for developing breast cancer. While there are association studies provided in the instant specification, none of the studies provide a correlation between the 2119 polymorphism and a predisposition for developing breast cancer.

The unpredictability of the art and the state of the prior art

There is a great deal of unpredictability in the association of mutations with particular diseases. Prior to filing of the instant application, the 2119T-C mutation is taught in the art by Izatt (Genes, Chromosomes and Cancer, Vol. 26, pages 286-294, December 1999). Izatt provides an analysis of rare variants detected in ATM gene (Table 3, page 290). The table illustrates the frequency in both patients and controls. The frequency in patients is 2/100 and the frequency in controls is 2/100. Thus, the frequency in normal individuals of the polymorphism is greater. The teachings of Izatt do not support the assertion of an association between the variation and a predisposition for developing breast cancer.

Post filing, the art has analyzed the 2119 mutation in various populations to determine whether an association between the mutation and breast cancer is present.

Dork et al. (Cancer Research, Vol. 61, pages 7608-7615, October15, 2001) teaches the S707P mutation in exon 15 was "two times more frequent in breast cancer patient and d five times more frequent in patients with bilateral disease than in random individuals (abstract). Upon reviewing the data provided in the article, the mutation was found in 28 heterozygotes with breast cancer (0.03) and 6 heterozygotes which were controls (0.01). The p-value was calculated at 0.05.

Spurdle et al (Breast Cancer Research, Vol. 4, R15, August 21, 2002) states that no evidence for association of ATM gene T2119C and risk of breast cancer was found.

Spurdle uses a Australian population-based case-control study to investigates Ser707Pro. The 2119C variant was found to be rare, occurring at frequencies of 1.4 and 1.3% in cases and controls (p=0.08). Spurdle concludes that no difference in genotype distribution between cases and controls was found and the TC genotype was not associated with increased risk of breast cancer. Spurdle acknowledges that three other studies reported the variant to be more common in breast cancer cases than in controls (page 3). Citing each of these three studies, Spurdle states that "our larger Australian population-based case and control samples were frequency-matched for age, and our study found no evidence for such an increased risk, before or after adjustment for measured risk factors on in the subset of Caucasian individuals. Spurdle states that "given the observed frequencies of greater than 1% for the variant alleles in our large control sample (n>600) and no large differences in allele frequency between the case and control groups, we believe these variants should be considered nonpathogenic polymorphisms. These variants are unlikely to be associated with even moderate risks of breast cancer" (page 5). Spurdle states that the study was of sufficient size to have 80% power at the 0.05 level of significance to detect an OR of 2.1 or more for the T2119C variant (page 5).

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to apply this association to individuals given the negative teachings of association in the art.

Reviewing articles have analyzed the number of times an association exists following the identification of an association in a small initial population. As noted by Ioannidis et al. (Nature Genetics, Vol. 29, pages 306-309, 2001), diversity is frequent between studies and that the results of the first study correlate only modestly with

subsequent research on the same association. The "first study often suggest a stronger genetic effect than is found by subsequent studies" which may be explained by "bias and genuine population diversity." Ioannidis states that the association from the first study gradually becomes less prominent or even disappears as more data is accumulated." Thus, sampling biases, publication bias, time-lag bias, underpowered studies is problematic such that "isolated statistical significance does not guarantee a genetic association."

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Guidance in the Specification.

The teachings of the specification do not establish that one could actually detect a polymorphism at 2119 of ATM as an indicator of breast cancer. Rather the teachings of the specification asserts that the 2119 mutation is present in both control and breast cancer individuals. The specification suggests that the mutation is present more frequently in normal individuals than in breast cancer patients. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. While one could conduct additional experimentation to determine whether, e.g., the 2119 polymorphism might be associated with e.g., breast cancer, the outcome of such research cannot be predicted, and such further research and experimentation are both unpredictable and undue. The data in the specification fails to provide any guidance for determining primary BC or bilateral breast cancer.

In the absence of guidance from the specification, one skill in the art may look to the teachings of the prior art for enablement of the claimed invention. However, the closest prior art does not provide support for the use of 2119 mutation as an indicator

for breast cancer. In fact, Izatt corroborates the teachings in the specification which suggest the presence of the polymorphism is not associated with breast cancer. Moreover, post filing date art has established that no clear correlation exists between the mutation and breast cancer despite large controlled studies. Thus, it is unpredictable as to whether one could successfully use the claimed invention, and given the fact that neither the specification nor the prior art provide evidence of a correlation or association between the 2119 polymorphism and breast cancer, it is further unpredictable as to whether any quantity of experimentation would allow one to practice the claimed invention. Accordingly, it would require undue experimentation for a skilled artisan to use the claimed invention. In light of the teachings in the prior art, and the general unpredictability concerning the association between 2119 and breast cancer, the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the presence of a possible association between the 2119 polymorphism and breast cancer, the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art and the specification provides insufficient guidance to overcome the lack of association between the polymorphism and the mutation. Thus given the claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define an association for screening a subject, the lack of guidance provided in the specification, and the absence of a working examples providing an association balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Conclusion

8. No claims allowable.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg

Jeanine Goldberg
Patent Examiner
September 12, 2003